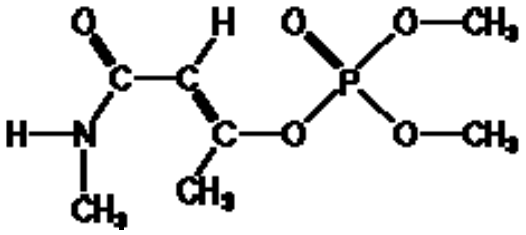
ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs)

PROPOSED

MONOCROTOPHOS (CAS Reg. No. 6923-22-4)



PREFACE

Under the authority of the Federal Advisory Committee Act (FACA) P. L. 92-463 of 1972, the National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances (NAC/AEGL Committee) has been established to identify, review and interpret relevant toxicologic and other scientific data and develop AEGLs for high priority, acutely toxic chemicals.

AEGLs represent threshold exposure limits for the general public and are applicable to emergency exposure periods ranging from 10 minutes to 8 hours. Three levels C AEGL-1, AEGL-2 and AEGL-3 C are developed for each of five exposure periods (10 and 30 minutes, 1 hour, 4 hours, and 8 hours) and are distinguished by varying degree of severity of toxic effects. The three AEGLs are defined as follows:

AEGL-1 is the airborne concentration (expressed as parts per million or milligrams per cubic meter [ppm or mg/m^3]) of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic, non-sensory effects. However, the effects are not disabling and are transient and reversible upon cessation of exposure.

AEGL-2 is the airborne concentration (expressed as ppm or mg/m^3) of a substance above which it is predicted that the general population, including susceptible individuals, could experience irreversible or other serious, long-lasting adverse health effects or an impaired ability to escape.

AEGL-3 is the airborne concentration (expressed as ppm or mg/m^3) of a substance above which it is predicted that the general population, including susceptible individuals, could experience life-threatening health effects or death.

Airborne concentrations below the AEGL-1 represent exposure levels that could produce mild and progressively increasing but transient and nondisabling odor, taste, and sensory irritation or certain asymptomatic, non-sensory effects. With increasing airborne concentrations above each AEGL, there is a progressive increase in the likelihood of occurrence and the severity of effects described for each corresponding AEGL. Although the AEGL values represent threshold levels for the general public, including susceptible subpopulations, such as infants, children, the elderly, persons with asthma, and those with other illnesses, it is recognized that individuals, subject to unique or idiosyncratic responses, could experience the effects described at concentrations below the corresponding AEGL.

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EXECUTIVE SUMMARY

Monocrotophos is an organophosphate insecticide originally used to control sucking, chewing and boring arthropods on cotton, sugarcane, peanuts, ornamental plants, and tobacco. It is no longer used in any registered pesticide products in the United States.

There are no inhalation toxicity data on monocrotophos in humans and inhalation data in animals are limited to lethality. Exposure-response data for nonlethal effects are not available.

Monocrotophos inhibits acetylcholinesterase (ChE) activity resulting in an excess of acetylcholine at neuronal synapses and myoneural junctions. Like other organophosphates, monocrotophos phosphorylates the esteratic subsite of the enzyme which, in turn, prevents the enzyme from deactivating acetylcholine. The overall result is an enhancement of cholinergic-mediated function (e.g., miosis, salivation, sweating, muscle fasciculations and tremors). Like other cholinesterase inhibitors, monocrotophos is very toxic and may exert its activity following oral, dermal, or inhalation exposure.

AEGL-1 values for monocrotophos are not recommended due to insufficient data.

Data were also insufficient regarding effects consistent with AEGL-2 tier severity. No exposure-response data were available that identified effects consistent with AEGL-2 tier severity or that enabled an assessment of an exposure-response relationship. The available studies provided lethality benchmarks but no individual or exposure-specific response data. Although one study reported that typical cholinergic responses were observed in all exposure groups, the severity of the responses was not specified and it was unknown as to which, if any, of the exposures were without lethal responses. In the absence of data consistent with the AEGL-2 tier, the AEGL-2 values were estimated as a 3-fold reduction of the AEGL-3 values under the assumption that the exposure-response curve for monocrotophos was very steep like that of other organophosphates.

The 1-hour LC_{50} of 94 mg/m^3 and 4-hour LC_{50} of 80 mg/m^3 (adjusted to 66.1 and 56.2 mg/m^3, respectively, to account for the 70.3% purity of the test article) for rats reported by Sachsse et al. (1974) were used as initial points-of-departure (POD) for derivation of AEGL-3 values. Lethality thresholds for these exposure durations were estimated as a 3-fold reduction of the adjusted 1-hr and 4-hr LC_{50} values; 22.0 mg/m^3 for 1-hour duration and 18.7 mg/m^3 for a 4-hour duration. Although data for monocrotophos are limited, this approach was justified by the fact that other organophosphates exhibit a steep exposure-response relationship, and it is assumed that monocrotophos having the same mode of action would likely exhibit a similar exposure-response relationship. The use of two duration-specific values within the AEGL duration span reflects the available data more than a default time scaling across the 10-minute to 8-hour time span.

Uncertainty factor application for monocrotophos AEGL development followed that for other organophosphate anticholinesterases. Specifically, the uncertainty factor for interspecies variability is 3 and the uncertainty factor for individual variability remains at the default value of 10. Chemical-specific data with which to assess species variability in the toxicity of inhaled

monocrotophos are unavailable. However, the variability in the toxicity of other organophosphate cholinesterase inhibitors is, in part, dependent upon the interaction with other less critical targets such as plasma ChE, carboxylesterases, and red blood cell ChE. In this respect, these cholinesterases may function as an effective repository for organophosphate ChE inhibitors and serve as a buffer against cholinergic-mediated adverse effects. Plasma ChE activity in humans is greater than that of mice and rats, and human plasma ChE represents a greater portion of blood ChE relative to animal species. Additionally, approximately 50% of total blood ChE activity in humans is in the form of the noncritical plasma ChE and baseline RBC ChE activity is higher in humans relative to animal species. These features collectively provide a protective advantage for humans with respect to organophosphate poisoning.

There are several arguments in support of retaining the default intraspecies uncertainty factor of 10 for monocrotophos. Genetic polymorphism has been shown for A-esterases (paraoxonase/arylesterase) in blood and liver of humans, known to provide some levels of protection against cholinesterase-inhibiting agents. This genetic variability may alter the protective effect of these esterases and individuals expressing forms with low hydrolyzing activity are considered to be more susceptible to organophosphate anticholinesterase poisoning. There is also evidence for gender and age-related variability in the toxic response to organophosphates. In the absence of chemical-specific data showing that monocrotophos would act contrary to other organophosphate cholinesterase inhibitors, an intraspecies uncertainty factor of 10 was retained.

Data with which to assess the exposure concentration-duration relationship are not available for monocrotophos. The concentration-exposure time relationship for many irritant and systemically acting vapors and gases may be described by $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5 (ten Berge et al. 1986). In the absence of definitive data, temporal scaling default exponents of n = 3 are typically applied when extrapolating to shorter time points and n = 1 when extrapolating to longer time points (NRC 2001).

The AEGL values for monocrotophos are summarized in Table S-1.

TABLE S 1. AEGL Values for Monocrotophos (mg/m^3)

Classification	10-min	30-min	1-h	4-h	8-h	Endpoint (Reference)
AEGL-1 (Nondisabling)	NR	NR	NR	NR	NR	Not recommended; insufficient data
AEGL-2 (Disabling)	0.43	0.31	0.24	0.21	0.10	AEGL-2 values estimated by a one-third reduction of AEGL-3 values
AEGL-3 (Lethality)	1.3	0.92	0.73	0.62	0.31	lethality threshold estimated as a 3-fold reduction of 1-hour and 4-hour rat LC_{50} values of 66.1mg/m^3 and 56.2 mg/m^3 (adjusted for 70.3% purity from 94 and 80 mg/m^3) to 22.0 and 18.8 mg/m^3 respectively) (Sachsse et al., 1974); UF=3x10; $C^n x\ t = k$, where n=1 or 3

NR: Not Recommended. Absence of AEGL-1 values does not imply that concentrations below the AEGL-2 are without effect.

Toxicity (cholinergic effects) may occur following dermal exposure to aerosols or vapors of monocrotophos.

References

NRC (National Research Council). 2001. Standing operating procedures for developing acute exposure guideline levels for hazardous chemicals. Committee on Toxicology, Board on Toxicology and Environmental Health Hazards, Commission on Life Sciences, National Research Council. National Academy Press, Washington, DC.

Sachsse, K., Ullmann, G., Voss, G., Hess, R. 1974. Measurement of inhalation toxicity of aerosols in small laboratory animals. In: Duncan, W.A.M., Ed. Experimental Model Systems in Toxicology and Their Significance in Man. Proceedings of the European Society for the Study of Drug Toxicity. XV: 239-251.

1. INTRODUCTION

Monocrotophos is an organophosphate insecticide originally used to control sucking, chewing and boring arthropods on cotton, sugarcane, peanuts, ornamental plants, and tobacco. It is no longer used in any registered pesticide products in the United States (ACGIH, 2002) although it is still used in other countries. The physical/chemical properties of monocrotophos are summarized in Table 1.

TABLE 1. Chemical and Physical Data for Monocrotophos

Parameter	Value	Reference
Synonyms	O,O-dimethyl O-(2-methyl-carbamoyl-1-methyl-vinyl) phosphate; Azodrin®; dimethyl 2-methylcarbamoyl-1-methylvinyl phosphate; Monocron®; Nuvacron®	Sachsse et al., 1974; ACGIH, 2002
Chemical formula	$C_7H_{14}NO_5P$	ACGIH, 2002
Molecular weight	223.2	ACGIH, 2002
CAS Registry No.	6923-22-4	ACGIH, 2002
Physical state	Liquid	ACGIH, 2002
Solubility in water	Miscible	ACGIH, 2002
Vapor pressure	1.0×10^{-6} mm Hg @ 20°C	Sachsse et al., 1974
Density	1.24 g/cm^3 @ 20°C	Sachsse et al., 1974
Boiling point/Melting point	125 °C/54-55 °C	ACGIH, 2002
Conversion factors in air*	1 ppm = 9.13 mg/m^3 1 mg/m^3 = 0.11 ppm	ACGIH, 2002

* Monocrotophos testing used aerosols and, therefore, conversion to ppm was not applied

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

No data are available regarding human mortality following inhalation exposure to monocrotophos.

2.2 Nonlethal Toxicity

Data regarding inhalation exposure of humans to monocrotophos are not available.

2.3. Developmental/Reproductive Effects

Data on potential developmental/reproductive toxicity of monocrotophos in humans were not available.

2.4. Genotoxicity

No information regarding potential genotoxicity of monocrotophos in humans was available.

2.5. Carcinogenicity

No information regarding the carcinogenic potential of monocrotophos in humans was available.

2.6. Summary

No information regarding inhalation toxicity of monocrotophos in humans was available.

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

3.1.1 Rats

In a study by Sachsse et. al. (1974), groups of nine male and nine female rats (160-180 g; SPF) were exposed to monocrotophos (technical; 70.3% purity) for 1 or 4 hours. Post exposure observation was 7 days. A Cascade Impactor was used for sampling the test atmospheres and the aerosol concentrations and size determinations were determined using gravimetry (Mettler precision balance) and sampling membrane filters. The mass median aerodynamic diameter (MMAD) was 2-7 μm. The filters containing the pesticide were also analyzed using an automated cholinesterase-inhibition method. The 1-hour LC_{50} was 94 mg/m^3 (95% confidence limit: 60-146 mg/m^3) and the 4-hour LC_{50} value was 80 mg/m^3 (no confidence limits reported). The exposure-response data used to calculate these values were not provided in the report.

The ACGIH (2002) cited a 4-hour LC_{50} of 63 mg/m^3 for rats but noted that no details were available.

Newell and Dilley (1978) reported on an acute inhalation study in which groups of 10 male or female Sprague-Dawley rats were exposed to technical grade monocrotophos (Azodrin®; purity 61-64% as determined by gas chromatography following each inhalation exposure) for 1 hour. Exposure concentrations were 97, 151, 210, and 308 mg/m^3 as determined by gas chromatography. Aerosols were generated with either a pneumatic or ultrasonic generator. Aerosol size ranged from 0.3 to 3.0 μm. The animals were observed for 14 days post exposure. Although exposure response data were not provided, 1-hour LC_{50} values of 163 and 176 mg/m^3 were reported for males and females, respectively. Information regarding time of death was not provided. It was reported that all exposed animals exhibited signs of toxicity consistent with cholinergic poisoning (salivation, lacrimation, defecation, urination, muscle fasciculation).

3.1.2 Summary of Lethal Toxicity in Animals

Animal lethality data are limited to rat LC_{50} values (Table 2). However, the sources for these values did report the exposure-response data used for derivation of the lethality benchmarks.

TABLE 2. Mortality in Rats Following Acute Inhalation Exposure to Monocrotophos		
Exposure Value (mg/m^3)	**Comments**	**Source**
1-hr LC_{50}: 94 4-hr LC_{50}: 80	♂ and ♀; 18 rats/group, 70.3% technical grade ♂ and ♀; 18 rats/group, 70.3% technical grade	Sachsse et. al. 1974
4-hr LC_{50}: 63	no details; original study unavailable	ACGIH, 2002
1-hr LC_{50}: 163 1-hr LC_{50}: 176	♂; 10 rats/group, 61-64% technical grade ♀; 10 rats/group, 61-64% technical grade	Newell and Dilley, 1978

3.2. Nonlethal Toxicity

3.2.1. Rats

In the study by Newell and Dilley (1978), rats exposed for one hour to monocrotophos at concentrations ranging from 97 to 308 mg/m^3 exhibited signs of cholinergic poisoning (lacrimation, salivation, defecation, muscle fasciculations). However neither exposure-response data nor severity/incidence data were provided, and it was not stated which, if any, of the exposures were without lethality.

3.3. Developmental/Reproductive Effects

No information is available in the open literature regarding potential developmental and reproductive toxicity of monocrotophos following inhalation exposure.

3.4. Genotoxicity

Information regarding the genotoxicity of monocrotophos following inhalation exposure is not available.

3.5. Carcinogenicity

Information regarding the carcinogenicity of monocrotophos following inhalation exposure is not available.

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

Mücke (1994) reviewed the metabolism of monocrotophos in animals. The information pertains to oral and dermal routes; no data on metabolism and disposition were available for inhaled monocrotophos. Absorption is rapid and complete following oral administration. Monocrotophos and its metabolites are widely distributed although concentrations tend be greatest in tissues and organs associated with elimination processes. There is no evidence for sequestration or bioaccumulation. Monocrotophos is metabolized via N-demethylation, O-demethylation, and by cleavage of the vinyl phosphate bond. Metabolism is complete with all carbon atoms having potential to enter the carbon pool. Urinary excretion accounts for 70-90%

of the dose while less than 10% is excreted in the feces. Carbon dioxide is eliminated via the lungs.

4.2. Mechanism of Toxicity

Monocrotophos inhibits acetylcholinesterase activity resulting in an excess of acetylcholine at neuronal synapses and myoneural junctions. Like other organophosphates, monocrotophos phosphorylates the esteratic subsite of the enzyme which, in turn, prevents the enzyme from deactivating acetylcholine (Taylor, 1985). The overall result is an enhancement of cholinergic-mediated function (e.g., miosis, salivation, sweating, muscle fasciculations and tremors).

4.3. Structure-Activity Relationships

The mode of action of organophosphates is inactivation of cholinesterase. Although all organophosphate ChE inhibitors have the same mode of action, their potency and physicochemical properties vary. The physicochemical differences will also affect environmental persistence and metabolic fate. In the absence of relative potency data, development of AEGL values for monocrotophos by analogy to other organophosphates would be tenuous.

4.4. Other Relevant Information

4.4.1. Species Variability

As an organophosphate cholinesterase inhibitor, the mode of action of monocrotophos (inhibition of acetylChE at neuromuscular junctions and in the CNS) will be the same across species and toxic responses will be qualitatively similar. Variability in toxicity would likely be a function of dosimetric factors and the extent of interaction of monocrotophos with other less critical targets such as plasma ChE, carboxylesterases, and red blood cell ChE (see Section 7.3 for greater detail).

4.4.2. Susceptible Populations

Individual variability in plasma ChE activity is well documented (NRC, 2003). This variability includes age-related differences (neonates are more susceptible than are adults), gender differences (females tend to have lower plasma and red blood cell ChE activity) and genetically determined variations in plasma ChE activity. This genetic variability (sometimes resulting in greatly reduced activity of plasma ChE) may impart deficiencies in ability to detoxify organophosphates such as monocrotophos. Additionally, polymorphic variability in A-esterases (paraoxonase/arylesterase) may also contribute to individual variability in organophosphate ester detoxification processes (NRC, 2003) (see Section 7.3 for greater detail).

4.4.3. Concurrent Exposure Issues

Both concurrent exposure to other organophosphates and simultaneous exposure via other exposure routes would be of concern.

5. DATA ANALYSIS FOR AEGL-1

5.1. Human Data Relevant to AEGL-1

No human data relevant to derivation of AEGL-1 values were available.

5.2. Animal Data Relevant to AEGL-1

No animal data were located in the open literature to assess AEGL-1 severity responses following acute inhalation exposure to monocrotophos.

5.3. Derivation of AEGL-1 Values

Data are insufficient for derivation of AEGL-1 values for monocrotophos (Table 3).

TABLE 3. AEGL-1 Values for Monocrotophos

Classification	10-min	30-min	1-h	4-h	8-h
AEGL-1	NR	NR	NR	NR	NR

NR: Not Recommended. Absence of AEGL-1 values does not imply that concentrations below the AEGL-2 are without effect.

6. DATA ANALYSIS FOR AEGL-2

6.1. Human Data Relevant to AEGL-2

There are no human data regarding AEGL-2 severity effects from inhalation exposure to monocrotophos.

6.2. Animal Data Relevant to AEGL-2

There are no exposure-response data in animals for AEGL-2 severity effects. The available studies provided lethality benchmarks but no individual or exposure-specific response data. Newell and Dilley (1978) reported that typical cholinergic responses were observed in all exposure groups but did not specify the severity of the responses. Also, it is uncertain as to which, if any, of the exposures were without lethal responses. It was implied, however, that surviving animals in each group completely recovered.

6.3. Derivation of AEGL-2 Values

Experimental data are unavailable with which to define a threshold for AEGL-2 severity effects. In the absence of data consistent with the AEGL-2 tier, the AEGL-2 values were estimated as a 3-fold reduction of the AEGL-3 values. This approach is justified by the fact that other organophosphates exhibit a steep exposure-response relationship (for example; for methyl parathion, the mortality rate in rats increases from 20% to 90% with only a 1.5-fold increase in dose). It is assumed that monocrotophos having the same mode of action and target would likely exhibit a similar exposure-response relationship. Values are shown in Table 4.

TABLE 4. AEGL-2 Values for Monocrotophos (mg/m^3)					
Classification	**10-min**	**30-min**	**1-h**	**4-h**	**8-h**
AEGL-2	0.43	0.31	0.24	0.21	0.10

7. DATA ANALYSIS FOR AEGL-3

7.1. Human Data Relevant to AEGL-3

No human data were available for derivation of AEGL-3 values for monocrotophos.

7.2. Animal Data Relevant to AEGL-3

Animal data relevant to derivation of AEGL-3 values are limited to studies (Sachsse et al., 1974; Newell and Dilley, 1978) in rats providing LC_{50} values but no exposure-response data (Table 2). The studies were well conducted and used adequate protocols but used technical grade monocrotophos with purity ranging from 61-70%. There is an approximately two-fold difference in 1-hr LC_{50} values from the Sachsse et al. (1974) report and that from the Newell and Dilley (1978) report. It is uncertain if this difference was due to the difference in purity of the test material.

7.3. Derivation of AEGL-3 Values

The 1-hour LC_{50} of 94 mg/m^3 and 4-hour LC_{50} of 80 mg/m^3 for rats reported by Sachsse et al. (1974) were used as initial points-of-departure (POD) for derivation of AEGL-3 values. These values were adjusted to 66.1 and 56.2 mg/m^3 to account for the 70.3% reported purity of the test article. Lethality thresholds were then estimated as a 3-fold reduction of these values; 22.0 mg/m^3 for 1-hour duration and 18.7 mg/m^3 for a 4-hour duration. Although data for monocrotophos are limited, the approach assuming a 3-fold reduction of the LC_{50} as a lethality threshold estimated is justified by the fact that other organophosphates exhibit a steep exposure-response relationship (for example; for methyl parathion, the mortality rate in rats increases from 20% to 90% with only a 1.5-fold increase in dose). It is assumed that monocrotophos having the same mode of action would likely exhibit a similar exposure-response relationship. The use of two duration-specific values within the AEGL duration span reflects the available data more than a default time scaling across the 10-minute to 8-hour time span.

Uncertainty factor application for monocrotophos AEGL development followed that for other organophosphate anticholinesterases (nerve agents, parathion, methyl parathion) with justifications being similar. Specifically, the uncertainty factor for interspecies variability is 3 and the uncertainty factor for individual variability remains at the default value of 10.

Chemical-specific data with which to assess species variability in the toxicity of inhaled monocrotophos are unavailable (data are limited to rats). However, the variability in the toxicity of other organophosphate cholinesterase inhibitors is, in part, dependent upon the interaction with other less critical targets such as plasma ChE, carboxylesterases, and red blood cell ChE. These cholinesterases may function as an effective repository for organophosphate ChE inhibitors thereby acting as a buffer against cholinergic-mediated adverse effects. It has been reported that plasma ChE activity in humans is twice that of mice and four times that of rats

(Cohen et al., 1971). It is important to note that human plasma ChE represents a greater portion of blood ChE relative to animal species (Wills, 1972; Osweiler et al., 1985; Cohen et al., 1971); specifically, approximately 50% of total blood ChE activity in humans is in the form of the noncritical plasma ChE (Osweiler et al., 1985). Furthermore, baseline RBC ChE activity is higher in humans relative to animal species (Ellin, 1981) which provides an additional protective advantage.

There are several arguments in support of retaining the default intraspecies uncertainty factor of 10 for monocrotophos. The underlying mechanism of organophosphates is inhibition of cholinesterase by phosphorylation of the esteratic site of the enzyme. Cholinesterases in the blood and tissues are known to be instrumental in limiting the amount of organophosphate compounds reaching critical targets such as brain ChE and acetylChE at cholinergic synapses (Parkinson and Ogilvie, 2008). Genetic polymorphism has been shown for A-esterases (paraoxonase/arylesterase) in blood and liver of humans (Cashman et al., 1996). This variability is relevant considering that the magnitude of the interaction of organophosphates with A-esterases may alter the aforementioned protective effect of these esterases. Yamasaki et al. (1997) reported that individuals expressing forms with low hydrolyzing activity are considered to be more susceptible to organophosphate anticholinesterase poisoning. Morgan (1989) noted that about 3% of individuals possess genetically determined low levels of plasma cholinesterase and that these individuals may exhibit greater sensitivity to some anticholinesterase compounds. Additionally, evidence for gender and age-related variability in the toxic response to organophosphates had been reported for humans (Shanor et al., 1961; Wills, 1972; Yokoyama et al., 1998) and animals (Mioduszewski et al., 2000, 2001, 2002a,b). In the absence of chemical-specific data showing that monocrotophos would act contrary to other organophosphate cholinesterase inhibitors, an intraspecies uncertainty factor of 10 was retained.

Data with which to assess the exposure concentration-duration relationship are not available for monocrotophos. The concentration-exposure time relationship for many irritant and systemically acting vapors and gases may be described by $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5 (ten Berge et al. 1986). In the absence of definitive data, temporal scaling default exponents of n = 3 are typically applied when extrapolating to shorter time points and n = 1 when extrapolating to longer time points (NRC 2001).

The AEGL-3 values for monocrotophos are shown in Table 5 and their derivation is presented in Appendices A and C.

TABLE 5. AEGL-3 Values for Monocrotophos (mg/m^3)

Classification	10-min	30-min	1-h	4-h	8-h
AEGL-3	1.3	0.92	0.73	0.62	0.31

8. SUMMARY OF AEGLs

8.1. AEGL Values and Toxicity Endpoints

The AEGL values for monocrotophos are shown in Table 6. Data were unavailable with which to derive AEGL-1 and AEGL-2 values for monocrotophos. AEGL-1 values were not recommended. Inhalation toxicity data for monocrotophos were limited to only one species (rat) and consisted of free-standing, somewhat conflicting 1-hour and 4-hour LC_{50} values. The

absence of exposure-response data precluded development of effect-specific AEGL-2 values, therefore these values were estimated as a one-third reduction of AEGL-3 values under the assumption that the exposure-response curve exhibits a steep slope typical of organophosphates. The AEGL-3 values were based upon a 3-fold reduction of 1-hour and 4-hour LC_{50} values; the former used as the POD for the 10-minute, 30-minute, and 1-hour AEGL-3 values and the latter used as the POD for the 4-hour and 8-hour AEGL-3 values.

TABLE 6. AEGL Values for Monocrotophos (mg/m^3)

Classification	10-min	30-min	1-h	4-h	8-h
AEGL-1 (Nondisabling)	NR	NR	NR	NR	NR
AEGL-2 (Disabling)	0.43	0.31	0.24	0.21	0.10
AEGL-3 (Lethality)	1.3	0.92	0.73	0.62	0.31

NR: Not Recommended. Absence of AEGL-1 values does not imply that concentrations below the AEGL-2 are without effect.
Toxicity (cholinergic effects) may occur following dermal exposure to aerosols or vapors of monocrotophos.

8.2. Comparisons with Other Standards and Guidelines

Standards and guidelines for monocrotophos are limited to an ACGIH TLV-TWA and a MAC (Table 7).

TABLE 7. Extant Standards and Guidelines for Monocrotophos (mg/m^3)

Guideline	Exposure Duration				
	10 min	30 min	1 h	4 h	8 h
AEGL-1	NR	NR	NR	NR	NR
AEGL-2	0.43	0.31	0.24	0.21	0.10
AEGL-3	1.3	0.92	0.73	0.62	0.31
TLV-TWA (ACGIH)[a]					0.05
MAC-Peak Category (The Netherlands)[b]					0.25

[a] ACGIH TLV-TWA (American Conference of Governmental Industrial Hygienists, Threshold Limit Value - Time Weighted Average) (ACGIH, 2008) is the time-weighted average concentration for a normal 8-hour workday and a 40-hour work week, to which nearly all workers may be repeatedly exposed, day after day, without adverse effect.

[b] MAC (Maximaal Aanvaaarde Concentratie [Maximal Accepted Concentration - Peak Category]) (SDU Uitgevers [under the auspices of the Ministry of Social Affairs and Employment], The Hague, The Netherlands 2000) is defined analogous to the ACGIH-Ceiling.

8.3. Data Adequacy and Research Needs

Inhalation toxicity data for monocrotophos are limited to free-standing LC_{50}values in rats. Exposure-response data for these lethality values were not available and no data were available for other than lethal effects. Data on non-lethal effects would allow for reassessment and validation of the AEGL values for monocrotophos.

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APPENDIX A: Derivation of AEGL Values

Derivation of AEGL-1 Values for Monocrotophos

AEGL-1 values are not recommended (NR) for monocrotophos due to insufficient data. Absence of AEGL-1 values does not imply that concentrations below the AEGL-2 are without effect.

Derivation of AEGL-2 Values for Monocrotophos

Experimental data are unavailable with which to define a threshold for AEGL-2 severity effects. In the absence of data consistent with the AEGL-2 tier, the AEGL-2 values were estimated a s a 3-fold reduction of the AEGL-3 values.

10-min AEGL-2 $1.3\ mg/m^3 \div 3 = 0.43\ mg/m^3$

30-min AEGL-2 $0.92\ mg/m^3 \div 3 = 0.31\ mg/m^3$

1- h AEGL-2 $0.73\ mg/m^3 \div 3 = 0.24\ mg/m^3$

4-h AEGL-2 $0.62\ mg/m^3 \div 3 = 0.21\ mg/m^3$

8-h AEGL-2 $0.31\ mg/m^3 \div 3 = 0.10\ mg/m^3$

Derivation of AEGL-3 Values for Monocrotophos

Key Study:	Sachsse, K., Ullmann, G., Voss, G., Hess, R. 1974. Measurement of inhalation toxicity of aerosols in small laboratory animals. In: Duncan,W.A.M., ed. Experimental Model Systems in Toxicology and Their Significance in Man. Proceedings of the European Society for the Study of Drug Toxicity. XV: 239-251.
Critical effect:	The 1-hour and 4-hour rat LC_{50} values of 94 mg/m^3 and 80 mg/m^3 were adjusted for 70.3% purity of the test article to 66.1 mg/m^3 and 56.2 mg/m^3. A 3-fold reduction of these values to 22.0 mg/m^3 and 18.8 mg/m^3, respectively, served as the final point-of-departure (POD) for AEGL-3 derivation.
Time scaling:	Data with which to assess the exposure concentration-duration relationship are not available. The concentration-exposure time relationship for many irritant and systemically acting vapors and gases may be described by $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5 (ten Berge et al. 1986). In the absence of definitive data, temporal scaling default exponents of n = 3 are typically applied when extrapolating to shorter time points and n = 1 when extrapolating to longer time points (NRC 2001).
Uncertainty factors:	Total uncertainty factor 30. Interspecies: 3; Chemical-specific data with which to assess species variability in the toxicity of inhaled monocrotophos are unavailable (data are limited to rats). The variability in the toxicity of monocrotophos and other organophosphate cholinesterase inhibitors is, in part, dependent upon the interaction with other less critical targets such as plasma ChE, carboxylesterases, and red blood cell ChE. In this respect, these cholinesterases may function as an effective repository for organophosphate ChE inhibitors and serve as a buffer against cholinergic-mediated adverse effects. Plasma ChE in humans is twice that of mice and four times that of rats. Human plasma ChE also accounts for a greater portion of blood ChE relative to animal species; specifically, approximately 50% of total blood ChE activity in humans is in the form of the noncritical plasma ChE. Further, baseline RBC ChE activity is higher in humans relative to animal species which provides an additional protective advantage. Intraspecies: 10; Genetic polymorphisms in some individuals result in enzymes with low hydrolyzing activity and greater susceptibility to organophosphate poisoning. About 3% of individuals possess genetically determined low levels of plasma cholinesterase that may result in greater sensitivity to anticholinesterase compounds. These contribute to a decreased potential for preventing interaction of cholinesterase inhibitors

with critical targets. Additionally, evidence for gender and age-related variability in the toxic response to organophosphates has been reported for humans and animals.

Modifying Factor: None applied

Calculation: Lethality threshold estimate:
1-hr LC_{50} of 66 mg/m^3 (adjusted for 70.3% purity) ÷ 3 = 22.0 mg/m^3
4-hr LC_{50} of 56 mg/m^3 (adjusted for 70.3% purity) ÷ 3 = 18.7 mg/m^3

For 10-min. and 30-min values: $C^n \times t = k$, where n=3
(22.0 mg/m^3)^3 x 1 hr = 10,648 mg·hrs/m^3

For 8-h AEGL-3: $C^n \times t = k$, where n=1
(18.7 mg/m^3)^1 x 4 hrs = 74.8 mg·hrs/m^3

10-min AEGL-3
(C mg/m^3)^3 x 0.1667 hrs = 10,648 mg·hrs/m^3
C^3 = 63,875 mg/m^3
C = 39.97 mg/m^3
C = 39.97 mg/m^3 ÷ 30 = 1.3 mg/m^3

30-min AEGL-3
(C mg/m^3)^3 x 0.5 hrs = 10,648 mg·hrs/m^3
C^3 = 21,296 mg/m^3
C = 27.72 mg/m^3
C = 27.72 mg/m^3 ÷ 30 = 0.92 mg/m^3

1- hr AEGL-3
(C mg/m^3) x 1 hr = 22 mg·hrs/m^3
C = 22 mg/m^3
C = 22 mg/m^3 ÷ 30 = 0.73 mg/m^3

4-hr AEGL-3
(C mg/m^3)^1 x 4 hrs = 74.8 mg·min/m^3
C = 18.70 mg/m^3
C = 18.70 mg/m^3 ÷ 30 = 0.62 mg/m^3

8-hr AEGL-3
(C mg/m^3)^1 x 8 hrs = 74.8 mg·min/m^3
C = 9.35 mg/m^3
C = 9.35 mg/m^3 ÷ 30 = 0.31 mg/m^3

APPENDIX B: Time Scaling Calculations

The relationship between dose and time for any given chemical is a function of the physical and chemical properties of the substance and the unique toxicological and pharmacological properties of the individual substance. Historically, the relationship according to Haber (1924), commonly called Haber=s Law or Haber=s Rule (i.e., $C \times t = k$, where C = exposure concentration, t = exposure duration, and k = a constant) has been used to relate exposure concentration and duration to effect (Rinehart and Hatch, 1964). This concept states that exposure concentration and exposure duration may be reciprocally adjusted to maintain a cumulative exposure constant (k) and that this cumulative exposure constant will always reflect a specific quantitative and qualitative response. This inverse relationship of concentration and time may be valid when the toxic response to a chemical is equally dependent upon the concentration and the exposure duration. However, an assessment by ten Berge et al. (1986) of LC_{50} data for certain chemicals revealed chemical-specific relationships between exposure concentration and exposure duration that were often exponential. This relationship can be expressed by the equation $C^n \times t = k$, where n represents a chemical specific, and even a toxic endpoint specific, exponent. The relationship described by this equation is basically in the form of a linear regression analysis of the log-log transformation of a plot of C vs t. ten Berge et al. (1986) examined the airborne concentration (C) and short-term exposure duration (t) relationship relative to death for approximately 20 chemicals and found that the empirically derived value of n ranged from 0.8 to 3.5 among this group of chemicals. Hence, the value of the exponent (n) in the equation $C^n \times t = k$ quantitatively defines the relationship between exposure concentration and exposure duration for a given chemical and for a specific health effect endpoint. Haber's Rule is the special case where $n = 1$. As the value of n increases, the plot of concentration vs time yields a progressive decrease in the slope of the curve.

The available data do not allow for empirical derivation of a temporal scaling factor (n) for monocrotophos. The concentration-exposure time relationship for many irritant and systemically acting vapors and gases may be described by $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5 (ten Berge et al. 1986). Data are unavailable with which to evaluate the exposure time-exposure concentration relationship and empirical derivation of the exponent, n, for the relationship $C^n \times t = k$ is not possible. In the absence of definitive data, temporal scaling default exponents of $n = 3$ are typically applied when extrapolating to shorter time points and $n = 1$ when extrapolating to longer time points (NRC 2001).

APPENDIX C: Derivation Summary Tables

1

AEGL-1 VALUES FOR MONOCROTOPHOS (mg/m^3)				
10 min	**30 min**	**1 h**	**4 h**	**8 h**
NR	NR	NR	NR	NR
Reference: Not applicable				
Test Species/Strain/Number: not applicable				
Exposure Route/Concentrations/Durations : not applicable				
Effects: not applicable				
Endpoint/Concentration/Rationale:				
Uncertainty Factors/Rationale: not applicable				
Modifying Factor: not applicable				
Animal to Human Dosimetric Adjustment: not applicable				
Time Scaling: not applicable				
Data Adequacy: Data are insufficient for derivation of AEGL-1 values for monocrotophos. Therefore, AEGL-1 values are not recommended. Absence of AEGL-1 values does not imply that concentrations below the AEGL-2 are without effect.				

2

1

AEGL-2 VALUES FOR MONOCROTOPHOS (mg/m^3)				
10 min	**30 min**	**1 h**	**4 h**	**8 h**
0.43	0.31	0.24	0.21	0.10
Reference. See AEGL-3 derivation				
Test Species/Strain/Number: See AEGL-3 derivation				
Exposure Route/Concentrations/Durations: NA				
Effects: AEGL-2 values derived by 3-fold reduction of AEGL-3 values				
Endpoint/Concentration/Rationale:				
Uncertainty Factors/Rationale: See AEGL-3 derivation				
Modifying Factor: See AEGL-3 derivation				
Animal to Human Dosimetric Adjustment: not applicable				
Time Scaling: NA				
Data Adequacy: See AEGL-3 derivation				

2

1

AEGL-3 VALUES MONOCROTOPHOS (mg/m^3)				
10 min	**30 min**	**1 h**	**4 h**	**8 h**
1.3	0.92	0.73	0.62	0.31

Reference: Sachsse, K., Ullmann, G., Voss, G., Hess, R. 1974. Measurement of inhalation toxicity of aerosols in small laboratory animals. In: Duncan, W.A.M., ed. Experimental Model Systems in Toxicology and Their Significance in Man. Proceedings of the European Society for the Study of Drug Toxicity. XV: 239-251.

Test Species/Strain/Sex/Number: SPF rats, strain not specified/9 males, 9 females per group

Exposure Route/Concentrations/Durations: inhalation, monocrotophos 70.3%; test group exposure concentrations not specified; MMAD 2-7 μm/ 1–hr or 4-hr exposure duration

Effects: lethality; 7-day observation period

Endpoint/Concentration/Rationale: The 1-hour and 4-hour rat LC_{50} values of 90 mg/m^3 and 80 mg/m^3 were adjusted to 66 and 56 mg/m^3, respectively, for purity; a 3-fold reduction to 22.0 and 18.7mg/m^3 served as as estimate of the lethality threshold and the final point-of-departure (POD) for AEGL-3

Uncertainty Factors/Rationale: 30

Interspecies: 3; Chemical-specific data with which to assess species variability in the toxicity of inhaled monocrotophos are unavailable (data are limited to rats). The variability in the toxicity of monocrotophos and other organophosphate cholinesterase inhibitors is, in part, dependent upon the interaction with other less critical targets such as plasma ChE, carboxylesterases, and red blood cell ChE. In this respect, these cholinesterases may function as an effective repository for organophosphate ChE inhibitors and serve as a buffer against cholinergic-mediated adverse effects. Plasma ChE activity in humans is twice that of mice and four times that of rats. Human plasma ChE also accounts for a greater portion of blood ChE relative to animal species; specifically, approximately 50% of total blood ChE activity in humans is in the form of the noncritical plasma ChE. Further, baseline RBC ChE activity is higher in humans relative to animal species which provides an additional protective advantage.

Intraspecies: 10; Genetic polymorphisms in some individuals result in enzymes with low hydrolyzing activity and greater susceptibility to organophosphate poisoning. About 3% of individuals possess genetically determined low levels of plasma cholinesterase that may result in greater sensitivity to anticholinesterase compounds. These contribute to a decreased potential for preventing interaction of cholinesterase inhibitors with critical targets. Additionally, evidence for gender and age-related variability in the toxic response to organophosphates has been reported for humans and animals.

Modifying Factor: none applied

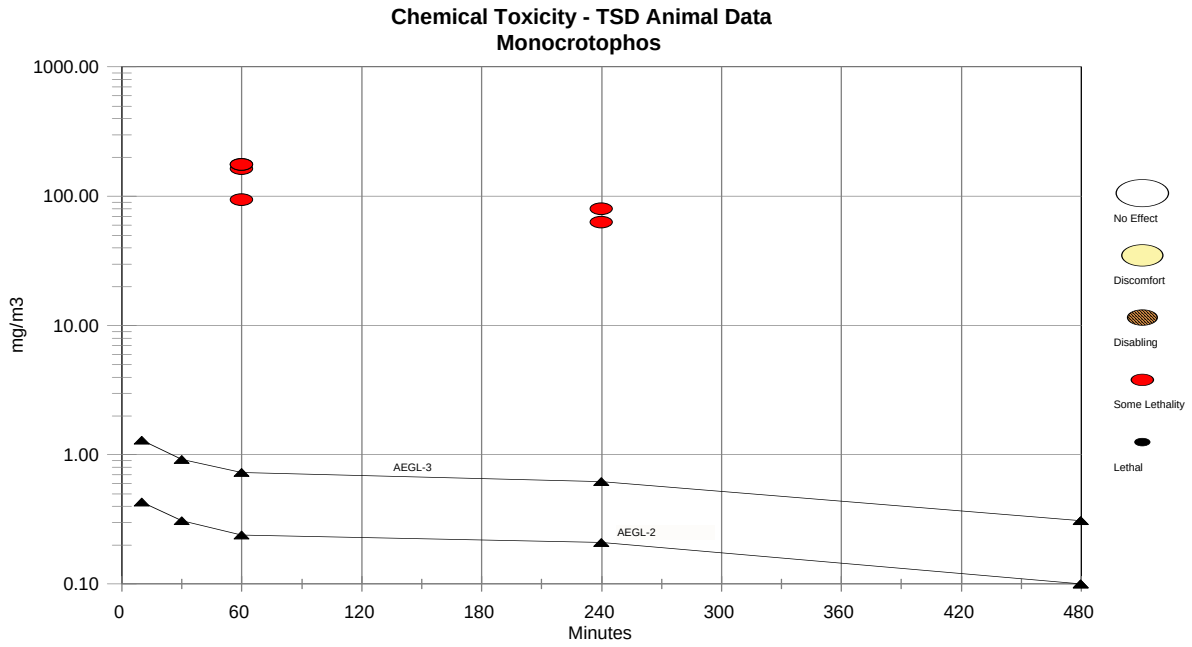
Animal to Human Dosimetric Adjustment: not applicable

Time Scaling: $C^n \times t = k$, where n=1or 3

Data Adequacy: marginal; data regarding the exposure-response relationship would allow for more defensible values.

2

APPENDIX D: Category Plot



Data are insufficient for derivation of AEGL-1 values for monocrotophos. Therefore, AEGL-1 values are not recommended. Absence of AEGL-1 values does not imply that concentrations below the AEGL-2 are without effect.

1

Monocrotophos

For Category 0 = No effect, 1 = Discomfort, 2 = Disabling, PL = Some Lethality, 3 = Lethal

Source	Species	Sex	# Exp.	mg/m^3	Minutes	Category	Comments
NAC/AEGL-1				NR	10	AEGL	
NAC/AEGL-1				NR	30	AEGL	
NAC/AEGL-1				NR	60	AEGL	
NAC/AEGL-1				NR	240	AEGL	
NAC/AEGL-1				NR	480	AEGL	
NAC/AEGL-2				0.43	10	AEGL	
NAC/AEGL-2				0.31	30	AEGL	
NAC/AEGL-2				0.24	60	AEGL	
NAC/AEGL-2				0.21	240	AEGL	
NAC/AEGL-2				0.10	480	AEGL	
NAC/AEGL-3				1.3	10	AEGL	
NAC/AEGL-3				0.92	30	AEGL	
NAC/AEGL-3				0.73	60	AEGL	
NAC/AEGL-3				0.62	240	AEGL	
NAC/AEGL-3				0.31	480	AEGL	
	rat	m&f	1	94	60	PL	LC50 (Sachsse et al., 1974)
	rat	m&f	1	80	240	PL	LC50 (Sachsse et al., 1974)
	rat	m&f	1	63	240	PL	unverified LC50 (ACGIH, 2002)
	rat	m	1	163	60	PL	LC50 males(Newell and Dilley, 1978)
	rat	f	1	176	60	PL	LC50 females(Newell and Dilley, 1978)

2